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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,855	10/31/2003	Jens Holm	04305/100M237-US1	9333

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EXAMINER	
TSAY, MARSHA M	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 11/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/698,855	HOLM ET AL.	
	Examiner	Art Unit	
	Marsha M. Tsay	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-75* is/are pending in the application.

4a) Of the above claim(s) *18,33-51,58,60-72,74 and 75* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,8-11,14,15,20-28,30-32,52-57,59 and 73* is/are rejected.

7)☒ Claim(s) *2-4,7,12,13,16,17,19 and 29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/22/04, 08/11/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election with traverse of Invention I, claims 1-17, 19-20, 21-32, 52-57, 59, and 73 in Paper No. 2, filed September 27, 2004 is acknowledged. The traversal is not found persuasive because each protein variant of a scaffold protein to a naturally occurring allergen is patentably distinct because it is drawn to a different polypeptide sequence and structure, and is therefore specific to a particular allergen. The reasons for being patentably distinct are also explained in the test of the restriction requirement.

The requirement is still deemed proper and is therefore made FINAL.

Claims 18, 33-51, 58, 60-72, 74-75 have been withdrawn from further consideration by the Examiner because these claims are drawn to non-elected inventions. Claims 1-17, 19-20, 21-32, 52-57, 59, and 73 are currently under examination.

Priority: The instant application was filed October 31, 2003. This application claims priority to provisional application, filed November 1, 2002, and to foreign application PA 2002 01686, filed November 1, 2002. The foreign application PA 2002 01686 has been submitted; therefore, the priority date is November 1, 2002.

Drawings

The drawings are objected to because in Fig. 26, "rMal d 1" (2620), should be labeled as "Mal d 1", because on pg. 20 of the specification, Fig. 26 has accession number 2620 identified with Mal d 1. It is not clear which accession

number correlates with which allergen. This is also noted in Figures 1, 2, etc. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The disclosure is objected to because of the following informalities: on pg. 36, the term "thirteen's" should be changed to "thirteenth"; on pg. 20, line 15 of the specification, the term "Mal d 1" (2781) should be changed to "rMal d 1"; on pg. 20, line 22 of the specification, the term "rMal d 1" (2620) should be corrected to "Mal d 1"; on pg. 32, line 7 of the specification, the term "datsabase" should be

corrected to "database"; on pg. 63, line 25 of the specification, the term "Mal d 1" (2781) should be changed to "rMal d 1".

It is noted that Applicants interchangeably label Mal d 1 as rMal d 1 and vice versa, in the specification, as well as in the figures (Fig. 1, 2, etc.). This is confusing because it is not known which strains of Mal d 1 are mutated and which are not, as well as which database number is correlated with the correct Mal d 1 variant. It is noted that the objections in the specification as set forth in the preceding paragraph do not encompass all the errors due to the mislabeling of rMal d 1 and Mal d 1. Applicants should make the appropriate corrections throughout the specification and figures.

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Protein Variants of Naturally Occurring Allergens.

Claim Objections

Claim 3 is objected to because of the following informalities: the term "10.000" should be changed to "10,000" to comply with the US numbering system.

Claim 30 is objected to because in the group consisting of the secondary mutations, the mutations K32X, E59X, and E95X are listed twice. The residues that are transcribed twice should be deleted.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5-6, 8, 11-12, 14, 25-28, 30-32, 53-54, 57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to a recombinant protein variant with the ability to induce a protective immune response to a naturally occurring allergen. The use of the term "protective" renders the claim unclear. It is hard to establish whether an immune response is protective or not because several factors need to be assessed, such as concentration of antigen, binding of antigen to specific antibodies, the number and type of antibodies stimulated, and the activation of B and T cells. The recombinant protein variant may induce an immune response, but to deem the reaction as protective renders the claim indefinite. It is acknowledged that on pg. 43 of the specification, Applicants do provide a definition of "protective" immune response, however, the definition is broad in view and is in the opinion of Applicants and what they believe constitutes a protective immune response. Claim 1 is drawn to a primary mutation of a scaffold protein wherein the mutated amino acid is identical or homologous to the corresponding residue on the naturally occurring allergen. It is unclear what the purpose of introducing an identical amino acid to a scaffold protein can serve. If the amino acid introduced is identical, then the scaffold protein will not be a

variant and will have the same properties as the naturally occurring allergen. In addition, it is unclear what a "homologous" amino acid is. Amino acids are traditionally grouped together based on hydrophibicity, hydrophilicity, acidity, and basicity and are not characterized by being homologous.

Claim 5 is drawn to a protein variant comprising of 2-50, 2-49, 3-25, 4-15 and 5-12 primary mutations. There is no sequence reference available so there are no residues available for the mutations to read on.

Claim 6 is drawn to a protein variant that has a level of amino acid identity of between 20 and 60% or 30 and 50% with a naturally occurring allergen. There is no sequence reference available to assess if the protein variant has the amino acid identity within the ranges specified.

Regarding claims 5-6, 8, 11, 14, 54, 57 the phrase "preferably" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "preferably"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

Claim 12 is drawn to a surface region having an area of about 600-900 A^2. The use of the term "about" renders the claim indefinite because while the area is limited by the numerical range 600-900, it also includes other limitations not set forth in the claim and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claims 25, 28, 30-32 are drawn to the mutations of a protein variant. The claims lists primary and secondary mutations but do not include a SEQ ID reference. It is unclear what the mutations are drawn to because as disclosed,

the mutations are drawn to any residue on any amino acid sequence. The claims should be corrected to include the relevant amino acid sequence to which the protein variant is drawn to because the polypeptide sequence is essential to the function of the invention.

Claims 25 and 26 are drawn to a primary mutation "Q76H". Claim 25 already discloses amino acid residue 76 as Glutamic Acid (E), therefore it is unclear which residue Q76H is referring to or if it is a transcription error and was listed twice.

Claims 26 and 27 are drawn to SEQ ID NO:2 and SEQ ID NO:3, respectively. It is unclear if the SEQ ID NO. depicts the amino acid sequence of the protein variant or if the mutations when introduced to the amino acid SEQ ID NO. forms the protein variant.

Claim 52 is drawn to a primary mutation of a scaffold protein wherein the mutated amino acid is identical or homologous to the corresponding residue on the naturally occurring allergen. Please see the claim 1, 112-2nd rejection, for the same issues regarding identical or homologous amino acids.

Claim 53 is drawn to a scaffold protein having a level of sequence identity with the naturally occurring allergen of between 30 and 50%. There is no sequence reference available, therefore it is unclear how a level of sequence identity can be established and assessed.

Claim 54 is drawn to a primary mutation of a scaffold protein wherein the mutated amino acid is identical or homologous to the corresponding residue on

the naturally occurring allergen. Please see the claim 1, 112-2nd rejection, for the same issues regarding identical or homologous amino acids.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5-6, 9-10, 20-22, 55-56, 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Valenta et al. (US 5583046). Valenta et al. teach recombinant protein variants that exhibit the same or similar antigenic properties as birch pollen P14, as well as to other allergens in the Fagales order, wherein the polypeptide comprises at least one epitope of these allergens (col. 2, lines 14-25, lines 63-67; claims 1, 9-10, 20-22). Valenta teach a computer search for proteins whose sequences share homology with birch P14 and a significant homology between P14 and a cytoskeletal protein, profilin, is present (col. 3, lines 56-63, col. 5, fig. 5, col. 6, fig. 12; claims 1, 20-22). Valenta et al. teach the expression of a protein having at least one epitope of the P14 allergen where the 3'-region of PC14 cDNA (bp 419-478) was cloned in the EcoRI site of lambda gt11 and expressed as an IgE-binding polypeptide (col. 8, lines 54-67; claims 1, 20-22). In Fig. 12 (col. 10, lines 31-47; claim 1), Valenta et al. teach IgE-binding capacity with nonrecombinant and recombinant P14 and human prolifin, where

cross-reactivity was shown for strips 1 (P14 and Bet v 1) and 2 (P14) (col. 6, lines 40-44). Valenta et al. teach methods of administration using P14 synthetic polypeptide allergens to hyposensitize or desensitize a mammal, either alone or with a pharmaceutically acceptable carrier (col. 11, lines 35-40; claims 55-56, 59).

Claims 1, 5-6, 8-9, 15, 20-24, 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Son et al. (Son et al., 1999, Eur. J. Nutr. 38 : 201-215). Son et al. teach recombinant protein variants from 12 Mal d 1 clones derived from seven different apple strains and from Bet v 1 clones (p. 203; claims 1, 9, 20-24). Mal d 1 and Bet v 1 share a degree of 55-68% amino acid sequence identity (p. 202 intro.). Son et al. teach the amino acid sequences of the different Mal d 1 clones and the minor deviations between the clones (p. 206 results, p. 207 fig. 2), as well as the differences in amino acid identity between the Bet v 1 clones (p. 208 fig. 3, p. 209 table 1). To study IgE binding and cross-reactivity, Son et al. teach mutated allergens of Mal d 1 and Bet v 1 by site-directed mutagenesis (p. 208; claims 1, 5-6, 15, 20-24, 52). Son et al. teach IgE binding capacity of the recombinant allergens and mutants of Mal d 1 and Bet v 1 by enzyme allergosorbent test wherein the recombinant allergens with high IgE binding are categorized in class 3-4 and those with decreased IgE binding are categorized in class 0-2 (p. 211 table 2; p. 212 table 3). Note in particular, the high IgE binding capacity of the Mal d 1 isoallergen clones GD26 and GS29 (p. 211, table 2; claim 1, 8).

Claims 54, 73 are rejected under 35 U.S.C. 102(b) as being anticipated by King et al (King et al. 2001 J. Immun. 166(10): 6057-6065). King et al. teach modified recombinant allergens with reduced allergenicity while retaining immunogenicity of the natural allergens. King et al. teach hybrid proteins consisting of a portion of a guest allergen of interest and a portion of a homologous protein. King et al. describe the function of the homologous protein as a scaffold to maintain the native structure of the guest allergen of interest (p. 6057). King et al. identify the guest allergen Ag 5 from yellow jacket is Ves v 5 and the homologous host allergen to be Pol a 5, a paper wasp venom protein (p. 6057). King et al. teach Ves v 5 and Pol a 5 have a sequence identity of 59% and several hybrids of the two proteins (p. 6058, fig. 1; claim 54). King et al. teach the recombinant Ag 5s and hybrids show nearly identical CD spectra as those of the natural Ag 5s (p. 6060, figure 4; claim 54). The results in Table IV show that the hybrids EA-PV_{1-46}, EA-PV_{1-155}, and EA-$PV_{156-204}$ induced hybrid-specific, as well as vespid Ag 5-specific, T cell responses (p. 6063, Table IV; claim 73).

Claim Objections

Claims 2-4, 7, 12-13, 16-17, 19, 29 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marsha M. Tsay whose telephone number is 571-272-2938. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

November 22, 2004

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER